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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,740	12/24/2003	Eiichi Iishi	1422-0619P	9686

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BIRCH STEWART KOLASCH & BIRCH  
PO BOX 747  
FALLS CHURCH, VA 22040-0747

EXAMINER
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HABTE, KAHSAY

ART UNIT	PAPER NUMBER
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1624

NOTIFICATION DATE	DELIVERY MODE
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02/12/2007

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/743,740

Applicant(s)

IISHI ET AL.

Examiner

Kahsay Habte

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**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 18 January 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 1-6.  
Claim(s) withdrawn from consideration: \_\_\_\_\_.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See memo.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

**ADVISORY ACTION**

1. The amendment filed 1/18/2007 under 37 CFR 1.116 in reply to the final rejection but prior to the date of filing a brief, will be entered but it is not deemed to place the application in condition for allowance because Applicants' arguments are not persuasive enough to overcome the obviousness-type double rejection raises in the previous Office Action (item 3).

Applicants argue "the melting point range of 114-116 °C which is sharp and differs from the melting point range of Kaspersen et al. by at least 7.8 °C.....the Examiner must take the description of Kaspersen et al. as being true unless there is some other valid reason to suspect that the description is false....the Examiner has provided no valid reason why Kaspersen et al. were able to make it through peer review with incorrect information." The examiner disagrees with applicant's argument. The examiner is using Kaspersen et al. as a source for the prior art rejection for the instant claims 1-6. The comment on "melting point difference" was made in the previous Office Action to rebut applicant's argument that claims 1-6 are patentable because of the melting point difference. In earlier response applicants argue, "Instant claims 5 and 6 recite that the mirtazapine crystals have a melting point of 114-116 °C. This is a distinction to the teaching of Kaspersen et al. which recite that the melting point of the mirtazapine product 1c is 123.8-125.8 °C." The examiner disagrees with applicant's argument. Applicants are focusing in the melting point difference that maybe less useful in overcoming the prior art rejection. Note that the melting point limitation is only in claims 5 and 6.

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In regard to Applicant's argument "The Examiner has agreed in the August 28, 2006 Interview that the process of Kaspersen et al. uses 'ordinary drying conditions' as is described in Example 8 in the present specification". Since the drying conditions are silent in Kaspersen it was discussed that applicants can dry the product under ordinary condition (see the Interview Summary below).

**During the interview, it was discussed that applicants can overcome the prior art rejection (Kaspersen et al.) by replicating Kaspersen that is disclosed at page 1066. Since the drying conditions are silent in Kaspersen, applicants can dry the crude product under ordinary conditions.**

Applicant' argue, "Example 8 of the present application and the invention of Kaspersen et al. are the same in that mirtazapine is recrystallized from a solvent mixture of methanol/water. Also, the Examiner will note that the mirtazapine of Example 8 was under ordinary conditions. In view of these similarities, it is appropriate for the Examiner to rely on the experimental data of Example 8 in the present specification to show the properties of the final mirtazapine crystals of the present invention which are dried under relatively stringent conditions". The examiner disagrees with applicant's argument "that Example 8 of the present application and the invention of Kaspersen et al. are the same in that mirtazapine is recrystallized from a solvent mixture of methanol/water".

The workup of Kaspersen et al. is as follows:

The product was extracted with ethyl acetate, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness to yield 950 mg (85%) of crude 1c. The crude 1c was purified

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by chromatography over Alox B (eluted with hexane/ethyl acetate 7:3, v/v) to yield 830 mg. For the final purification the product was treated twice with 100 mg of charcoal in n-hexane (containing 1% of methanol) followed by crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colourless crystals, m.p. 123.8-125.8 °C. No impurities were detectable either on TLC, HPLC or GC.

Example 8 of the present application is as follows:

In 4728 g of methanol was dissolved 1195.46 g of a crude mirtazapine (HPLC purity: 99.0%) at 0° to 5°C, and 12 g of decolorizing carbon was added thereto, and the mixture was stirred at 5°C for 15 minutes. This solution was filtered at 0° to 5°C. Thereafter, 4065 g of ion-exchanged water was introduced into the filtrate, and 100 mg of seed crystals were added thereto. Thereto was added in a thin stream 9707 g of ion-exchanged water at 0° to 10°C to allow crystallization. The mixture was stirred at 0° to 5°C for 1 hour, and crystals were filtered. The crystals were washed with a mixed solution (liquid temperature: 0° to 5°C) of 340 g of methanol and 1291 g of ion-exchanged water. The crystals were dried under reduced pressure (4 to 5.3 kPa) at 50° to 60°C so that the water content was attained to not more than 3.5% by weight. The crystals were pulverized with a pulverizer (hammer-mill), to give crystals of a mirtazapine hydrate having an average particle diameter of 20 gm.

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The workup of Kaspersen et al. is different from Example 8 of the present application in many ways. First of all, the ratio of methanol/water is different. In Kaspersen et al. it is 1:1, but in Example 8 it is almost 4:1. Secondly, the drying process in Example 8 is not under ordinary condition because of higher temperature and reduced pressure. In general, the drying conditions and work up of Example 8 in the specification is different from that of Kaspersen.

Even if Example 8 is similar to Kaspersen et al., applicants did not show that the product made from Example 8 would not necessarily provide mirtazapine crystals having (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours.

As discussed in the interview with Dr. Garth Dahlen, the only way to prove that the prior art compound is different from the instantly claimed crystal is by replicating Kaspersen and show that Kaspersen mirtazapine crystal is different from what is claimed. Applicants have to prove the product from Kaspersen et al. that is dried under ordinary condition would not necessarily provide mirtazapine crystals having (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours. Note that Applicant's compound has passed the test (i.e. the hygroscopic degree was not more than 0.6% by weight when

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the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours), but this test was not done on the prior art compound.

The period for reply continues to run 3 MONTHS from the date of the final rejection. Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a) accompanied by the appropriate fee. The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. A reply within the meaning of 37 CFR 1.113 or a request for a continued examination (RCE) in compliance with 37 CFR 1.114 must be timely filed to avoid abandonment of this application.

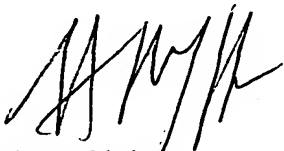
### ***Conclusion***

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Kahsay Habte', is written over the printed name.

Kahsay Habte  
Primary Examiner  
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February 6, 2007